

# **Smallpox Vaccine and Reproductive Health Outcomes**



## **Update from the National Smallpox Vaccine in Pregnancy Registry**

**Armed Forces Epidemiological Board  
11 May 2004**

**Margaret Ryan, MD, MPH**

# ***National Smallpox Vaccine in Pregnancy Registry Team***

## **DoD Birth and Infant Health Registry Team**

Shirley Chow, Ava Conlin, DO, MPH, William Honner, Robert Reed, MA, Cheryl Rudy, MPH, Tyler Smith, MS, Jennifer Strickler, Victor Stiegman, M Ryan, MD, MPH

## **Other DoD professionals**

John Grabenstein, RPh, PhD, MILVAX  
Renata Engler, MD, VHCC  
Peter Napolitano, MD, Madigan AMC  
Brian Pierce, MD, Darnall ACH, and *many others*

## **CDC professionals**

Jane Seward, MBBS, MPH, Kristin Kenyan, RN, MPH,  
Karen Broder, MD, MPH, Maria Cano, MD, MPH,  
Sandra Chaves, MD, MPH, Sonja Hutchins, MD, MPH, DrPH, Joseph Mulinare, MD, MSPH

## ***The National Smallpox Vaccine in Pregnancy Registry***

**Dryvax®** (Smallpox Vaccine, Dried, Calf Lymph Type)  
Wyeth Laboratories, Inc.

### **Pregnancy Category C**

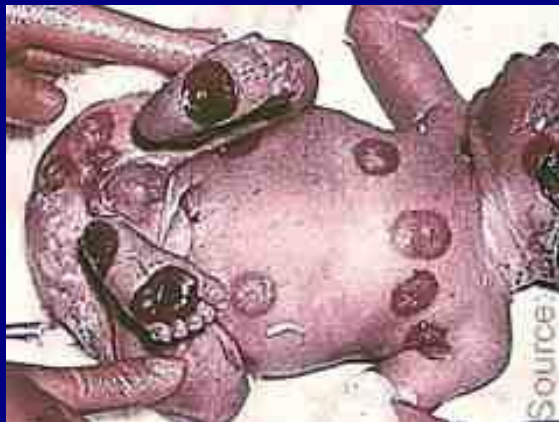
“Animal reproduction studies have not been conducted.... should not be given to pregnant women in non-emergency conditions... On rare occasions, almost always after primary vaccination, it has been reported to cause fetal infection. Fetal vaccinia usually results in stillbirth or death of the infant shortly after delivery. Vaccinia vaccine is not known to cause congenital malformations.”

- Some argue that pregnancy loss increased after vaccination (e.g., Bieniarz, et al, in Pol Tyg Lek 1956:11(52):2183-8)
- Only one report suggests increased malformations, club foot, with important limitations noted (Naderi in Obstet Gyn 1975:46(2):223-6)

# ***The National Smallpox Vaccine in Pregnancy Registry***

## **Fetal Vaccinia**

- Rare infection of the fetus.  
Incidence estimated at  $\sim 1/10,000$  exposed pregnancies. No cases reported in NYC in 1947 after  $\sim 173,000$  pregnant women vaccinated.
- When reported, exposures occurred at any stage of pregnancy. Outcome most often fetal death.



## ***The National Smallpox Vaccine in Pregnancy Registry***

- **Registry** developed because inadvertent exposures in pregnancy expected to occur when large numbers of young women (both military and civilian) were vaccinated in 2003.
- Registry justified because all effects of smallpox vaccine in pregnancy not well known or quantified.
- Registry, like those for rubella and varicella vaccines, actively follows all women exposed\* in pregnancy.

\*Vaccinated during pregnancy or within 42 days before conception,

or closely exposed to a vaccinee within 28 days after vaccination.

## ***The National Smallpox Vaccine in Pregnancy Registry***

- 236 women now actively followed in the Registry.

14 others are in Registry but <20 weeks EGA, so outcomes not described here. More than 50 others might be enrolled soon, as more data become available on them.

- 10 vaccinated as civilian healthcare workers
- 226 vaccinated as part of military service

No secondary-exposed cases described in outcomes to date.

- 177 (75%) exposed to vaccinia before a standard pregnancy test would have been positive.

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Among all 236 women in the Registry:**

- Mean age 23.3 years (range 18-41)
- 15 (6%) reported prior smallpox vaccination
- For 60%, this is first pregnancy (G<sub>1</sub>)

### **Among the 226 military women in Registry:**

- 78% are mid-enlisted ranks (E3-E5)
- 73% Army, 16% AirForce, 11% Navy/USMC/USCG
- 22% are Reservists
- 16% were vaccinated OCONUS
- 66% received other vaccine(s) in this pregnancy.

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Pregnancy Outcomes**

As of May 2004:

- 184 delivered (including one set twins, 185 infants)

- 14 are still pregnant (past 20 weeks EGA)

Pregnancy losses include:

- 2 ectopic pregnancies

- 11 elective abortions

- 23 spontaneous abortions (before 20 weeks EGA)

- 2 stillbirths (losses after 20 weeks EGA)



## ***The National Smallpox Vaccine in Pregnancy Registry***

### **More information on pregnancy losses**

Observed rate of ectopic pregnancy: 0.8%

Expected rate: 1.0 - 2.0%

Observed rate of spontaneous loss: 10.6 –  
11.2%

Expected rate: 9.0 – 30.0%

*Ventura et al. National Vital Statistics Reports 2003;51(4):1-18*

*Anderson et al. BMJ 2000;320-1708-12*

*Saraiya et al. Am J Epidemiol 1999;149(11):1025-9*

*Hammerslough CR. Public Health Report 1992;107(3):269-77*

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **More information on 25 spontaneous losses**

8 had history of previous SAB(s)

3 had bacterial infections and/or chorioamnionitis

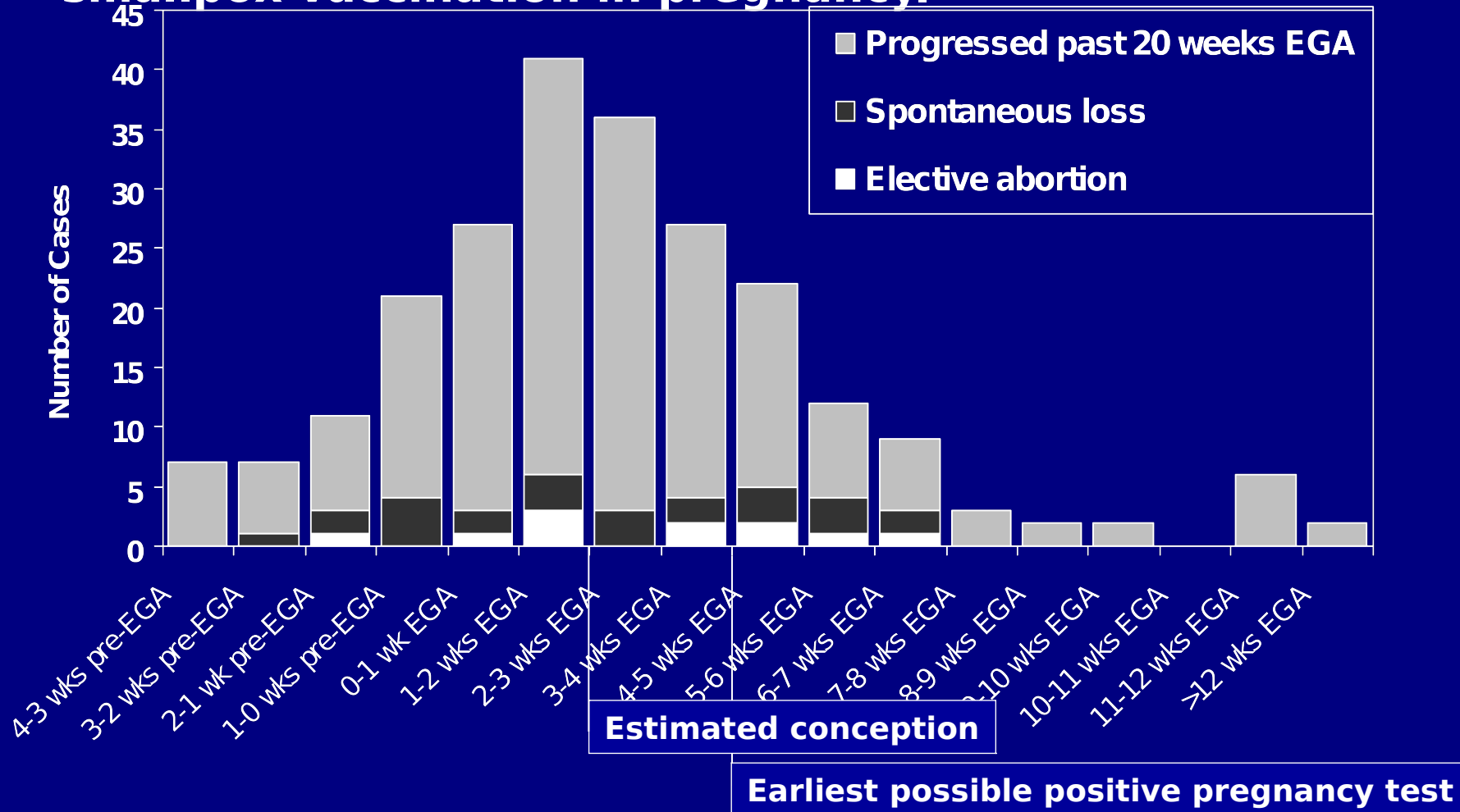
1 had incompetent cervix

2 stillbirths (losses after 20 weeks EGA)

- Spontaneous rupture of membranes at 21 weeks EGA, with subsequent chorioamnionitis
- Severely compressed nuchal cord at 34 weeks EGA, with subsequent fetal demise

4 early losses had products of conception tested for vaccinia virus: all negative

# **Pregnancy outcomes, by estimated gestational age (EGA) at vaccination, among 235 intrauterine pregnancies in women inadvertently exposed to smallpox vaccination in pregnancy.**



## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Adverse outcomes: maternal death**

31yo G<sub>12</sub>P<sub>4</sub> vaccinated at 5 weeks EGA, delivered a healthy infant by C-section at 37 weeks EGA. Developed fatal pulmonary embolus 2 weeks postpartum. Considered by ObGyn investigation as a post-operative complication; very unlikely related to previous vaccination.

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Infant outcomes among 185 births**

96 (52%) female, 88 (48%) male infants

175 full-term infants

10 pre-term (<36 weeks EGA)

Rate of pre-term births: 5.4%

Expected rate: 7.0 – 12.0%

*Yang et al. Am J Obstet Gynecol 2002 Mar;186(3):433-7.  
CDC. National Vital Statistics Reports 2003;52(10).*

# ***The National Smallpox Vaccine in Pregnancy Registry***

## **Infant outcomes: birth defects**

5 cases of major congenital anomalies

- 1 atrial septal defect (ASD)
- 1 ventricular septal defect (ASD)
- 1 isolated gastroschisis
- 1 isolated omphalocele
- 1 Beckwith-Weidemann Syndrome with omphalocele

Observed prevalence of birth defects: 2.7%

Expected prevalence: 3.0 – 4.0%

*CDC and NBDPN. Birth Defects Research (Part A)  
2003;67:729-816.*

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Infant outcomes: birth defects (continued)**

Observed ASD: 0.54%

Expected ASD: ~0.25%

Observed VSD: 0.54%

Expected VSD: ~0.37%

Observed gastroschisis: 0.54%

Expected gastroschisis: ~0.02%

Observed omphalocele: 0.54 (to 1.08)%

Expected omphalocele: ~0.03%

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Infant outcomes: SIDS**

2 infants died of Sudden Infant Death Syndrome

Full-term healthy infants, died at 7 weeks and 9 weeks of life

Observed rate: 1.08%

Expected rate: 0.04%

- Postmortem tests for vaccinia in both cases were negative.
- Expert review of cases revealed risk factors for SIDS, and relationship to maternal vaccination considered unlikely.



## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Infant outcomes: fetal vaccinia and/or fetal infection**

Maternal interviews reveal that at least 68 (37%) infants

have birth marks or other skin findings.

- None concerning for fetal vaccinia.

Saving cord blood and/or placenta for vaccinia testing consented by 5 parents of *healthy* infants to date.

- One recently positive for vaccinia by PCR, but discordant results noted between laboratories, and culture and other lab testing pending.

*Mother was vaccinated at 2 weeks EGA (at conception), delivered at 38 weeks without complications. Infant has no skin lesions or other findings; remains well at 2 weeks old*

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Conclusions**

Registry remains active, enrolling new cases weekly.

To date there has been:

- No observed increase in pregnancy losses,
- Some adverse outcomes noted (including 1 maternal death, 5 birth defects, and 2 SIDS cases), but interpretation limited by small numbers,
- No confirmed fetal vaccinia or vaccinia infection\*.

## ***The National Smallpox Vaccine in Pregnancy Registry***

### **Challenges and Future Directions**

- Close follow-up of Registry is warranted.
- Confirmation of vaccinia in placenta and cord blood of healthy infant will be difficult to interpret.
  - ? Part of a spectrum of infection, without overt disease?
  - ? Justifies more or less testing of healthy infants?
- Follow-up planned at infants' first birthdays.
  - Content, including developmental questions, being drafted.
  - ? Will findings justify longer follow-up?

Point of contact for questions,  
or to share/cite preliminary data:

Margaret Ryan, MD, MPH  
Director, DoD Center for Deployment Health  
Research  
NHRC Code 25  
San Diego, CA 92186

619-553-8097 or -9255  
[ryan@nhrc.navy.mil](mailto:ryan@nhrc.navy.mil)

# **Smallpox Vaccine and Reproductive Health Outcomes**



**Armed Forces Epidemiological Board  
11 May 2004**

**SUPPLEMENTARY  
INFORMATION**

- **Screening Forms to Prevent Exposures**

		<b>CHRONOLOGICAL RECORD OF MEDICAL CARE</b> <b>Smnopax Vaccination Initial Note Page 2 (2-Page Format)</b>	
This page to be completed by a health care provider			
1. Provider Assessment Date (MM/DD/YYYY) If Provider Assessment Date or Action Taken Immunization Date is blank.			
<b>2. Reason</b>  <input type="checkbox"/> Pre-  <input type="checkbox"/> Post-  <input type="checkbox"/> Post-  <input type="checkbox"/> Other		<b>CHRONOLOGICAL RECORD OF MEDICAL CARE</b> <b>Smnopax Vaccination Initial Note Page 2 (2-Page Format)</b>	
	This page may be completed by potential vaccine recipient 45687      1. Today/Date (MM/DD/YYYY)      2a. GENDER <input type="radio"/> Male <input type="radio"/> Female      2b. First day of last menstrual period      /      /		
3c. FEMALES: Were you last menstrual period normal and on time? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 3d. Are you currently breastfeeding? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure			
<b>4. Provider</b>  <input type="checkbox"/> Vacci  <input type="checkbox"/> Vacci  <input type="checkbox"/> Med  <input type="checkbox"/> Vacci  <input type="checkbox"/> Vacci  <input type="checkbox"/> Vacci  <b>5. IF NC</b>  <input type="checkbox"/> Lab  <input type="checkbox"/> Cons  <input type="checkbox"/> Follow  <input type="checkbox"/> Other	3. Could someone you LIVE WITH or YOU be pregnant? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 4. Do you have a child in the home with no year of age? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 5. Did you ever receive smallpox vaccine? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 5a. If YES: Were you vaccinated within the last 10 years? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 5b. IF UNSURE: Birth Year      First Year in Military (if applicable) <input type="text"/> <input type="text"/>		
	6. Have you ever had a serious problem after smallpox or other vaccination? (Describe below) <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 7. Do you currently have an illness with fever? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 8. Do you have a heart or vessel condition, such as angina, earlier heart attack, coronary artery disease, congestive heart failure, cardiomyopathy, stroke, "mini stroke," chest pain, trouble breathing or exertion? 9. Check EACH of the following conditions that apply to you: <input type="checkbox"/> Heart Condition before age 50 in mother, father, brother, sister <input type="checkbox"/> Smoke cigarettes now <input type="checkbox"/> High blood pressure <input type="checkbox"/> High cholesterol <input type="checkbox"/> Diabetes, or high blood sugar		
10. Do you allege to any of these products: streptococcus, streptomycin, polymyxin B, neomycin, latex? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 11. Do you NOW HAVE any of the following skin problems: Atopic Dermatitis? (Usually this skin condition involves an itchy, red, scaly rash that lasts more than 2 weeks. It often comes and goes.) <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 12. Do you NOW HAVE any of the following skin problems: Psoriasis (scaly skin rash), Burns (other than mild sunburn), Impetigo (skin infection), Uncontrolled Acne, Shingles (herpes zoster), Chickenpox, Darier's disease, Other Skin Condition (Describe below) <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 13. Do you have a problem or take a medication that affects the immune system? For example, do you have or take medication for HIV, AIDS, leukemia, lymphoma, or chronic liver problem; have or take medication for Crohn's disease, lupus, arthritis, or other immune disease; have had radiation or X-ray treatment (not routine X-rays) within the last 3 months; have EVER had a bone-marrow or organ transplant (or take medication for that); or have another problem that requires steroids, prednisone or a cancer drug for treatment. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 14. Do you currently being treated with steroid eye drops or ointment, or have you had recent eye surgery? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 15. Do you LIVE WITH anyone who NOW HAS or EVER HAD Eczema or Atopic Dermatitis? (Usually this skin condition involves an itchy, red, scaly rash that lasts more than 2 weeks. It often comes and goes.) <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 16. Do you LIVE WITH anyone who NOW HAS any of the following skin problems: Psoriasis (scaly skin rash), Burns (other than mild sunburn), Impetigo (skin infection), Uncontrolled Acne, Shingles (herpes zoster), Chickenpox, Darier's disease, Other Skin Condition (Describe below) <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 17. Do you LIVE WITH someone who has a problem or takes a medication that affects the immune system? For example do you have a close household contact who has or takes medication for HIV, AIDS, leukemia, lymphoma, or chronic liver problem; has or takes medication for Crohn's disease, lupus, arthritis, or other immune disease; has had radiation or X-ray treatment (not routine X-rays) within the last 3 months; has EVER had a bone-marrow or organ transplant (or take medication for that); or has another problem that requires steroids, prednisone or a cancer drug for treatment. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure 18. Do you have other questions or have other concerns you would like to discuss? <input type="radio"/> Yes <input type="radio"/> No NOTE: If you think you might have one of the many risk factors for HIV infection, we can arrange for HIV testing before vaccination. For FEMALES: If you might be pregnant, or likely to become pregnant, please let us know. You may need additional pregnancy testing.			
Explain "other," "unsure" or additional concerns (may use additional page)			
Last NA   First NA		Patient's Identification (May use for mechanical imprint)  RECORDS MAINTAINED AT: NAME/ADDRESS DATE OF BIRTH SPOCER NAME (or Sponsor SSN) RELATIONSHIP TO SPONSOR (or FAP) ORGANIZATION STATUS OFFICE	
First Name      MI      Last Name  Social Security Number			

# The National Smallpox Vaccine in Pregnancy Registry

- Intake Forms After Exposures Occur

National Smallpox Vaccine in Pregnancy Registry 4-11-03

5. Name of pregnant woman's primary care provider (if other than obstetrician/pregnancy provider):

Name of provider: \_\_\_\_\_  
Telephone: \_\_\_\_\_  
Email address: \_\_\_\_\_  
Organization: \_\_\_\_\_  
Mailing address: \_\_\_\_\_

National Smallpox Vaccine in Pregnancy Registry 4-11-03

6. Name of exposed pregnant woman:

Name of woman: \_\_\_\_\_  
Telephone: \_\_\_\_\_  
Email address: \_\_\_\_\_  
Mailing address: \_\_\_\_\_  
Street Address (Home): \_\_\_\_\_  
(if different from above) \_\_\_\_\_

Please note any plans for change of address or phone number in the next year.

7. Name of vaccine recipient:

Name of recipient: \_\_\_\_\_  
Telephone: \_\_\_\_\_  
Email address: \_\_\_\_\_  
Mailing address: \_\_\_\_\_  
Street Address (Home): \_\_\_\_\_  
(if different from above) \_\_\_\_\_

8. Name of vaccination site:

Name of site: \_\_\_\_\_  
Telephone: \_\_\_\_\_  
Email address: \_\_\_\_\_  
Mailing address: \_\_\_\_\_  
Street Address (Home): \_\_\_\_\_  
(if different from above) \_\_\_\_\_

9. Name of obstetrician or pregnancy provider:

Name of provider: \_\_\_\_\_  
Telephone: \_\_\_\_\_  
Email address: \_\_\_\_\_  
Organization: \_\_\_\_\_  
Mailing address: \_\_\_\_\_  
Street Address (Home): \_\_\_\_\_  
(if different from above) \_\_\_\_\_

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## VACCINE ADVERSE EVENT REPORTING SYSTEM (VAERS) Patient Identity Kept Confidential

### Supplemental Information for Smallpox Vaccine in Pregnancy Registry

Based on field-expedited word processor template, version 7 February 03 (based on Form VAERS-1), developed by the Military Vaccine Agency (MILVAX) Agency, U.S. Army Surgeon General's Office, 5111 Leesburg Pike, Suite 401, Falls Church, VA 22041.

Return to [code25@nhrc.navy.mil](mailto:code25@nhrc.navy.mil), or call DSN 553-9255, or 619-553-9255. POC: Dr. Margaret Ryan

Other ways to report Vaccine Adverse Events: [www.vaers.org](http://www.vaers.org), 800-822-7957, PO Box 1109, Rockville, MD 20849-1109

Clinical consultation on vaccination issues may be referred to the Vaccine Healthcare Centers, [www.vaccine.org](http://www.vaccine.org), 202-782-0411

These data will be used to increase understanding of adverse events following vaccination and will become part of Centers for Disease Control and Prevention Privacy Act System 09-20-0109, "Epidemiologic Studies and Surveillance of Disease Problems." Information identifying the persons who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

Patient Name (rank/service): \_\_\_\_\_

Patient SSN: \_\_\_\_\_

Patient date of birth: \_\_\_\_\_

Patient address (military unit and duty location): \_\_\_\_\_

Email and/or phone: \_\_\_\_\_

Form completed by: \_\_\_\_\_

Relation to patient: \_\_\_\_\_

Address: \_\_\_\_\_

Email and/or phone: \_\_\_\_\_

Date form completed: \_\_\_\_\_

Date smallpox vaccination given: \_\_\_\_\_

Facility name/location: \_\_\_\_\_

Date smallpox vaccine "take" assessed: \_\_\_\_\_

Was "take" evident? Yes No

Was pre-vaccination screening form completed? Yes No (If Yes, please provide copy)

Was pregnancy test done on day of vaccination? Yes No

Date pregnancy diagnosed: \_\_\_\_\_

Date of last normal menstrual period: \_\_\_\_\_

If ultrasound used for gestational age, provide results: \_\_\_\_\_

Method of birth control used at time of conception, if any: \_\_\_\_\_

Number of previous pregnancies: \_\_\_\_\_

List outcomes (with dates) of any previous pregnancies: \_\_\_\_\_

Was this the first smallpox vaccination for this patient? Yes No

If No, please provide approximate date(s) of any previous smallpox vaccinations: \_\_\_\_\_

Were any other vaccines administered during this pregnancy? Yes No

If Yes, please list other vaccines and dates administered: \_\_\_\_\_

Medical facility where patient will be followed (name/address/phone): \_\_\_\_\_

## ***The National Smallpox Vaccine in Pregnancy Registry***

- The overall pregnancy rate in vaccinees has been estimated to be at least 8 times lower than would be expected with no screening program in place.
- Interviews with several women suggest that increased counseling to avoid pregnancy after vaccination may have prevented some exposures.
- DoD and CDC expanded screening forms/processes in 2003 to prevent inadvertent exposures whenever possible.



# **Broader studies of smallpox vaccine and reproductive health**

PRMRP funded DoD study of smallpox vaccine and multiple reproductive health outcomes, including:

- Women vaccinated before pregnancy, and their pregnancy outcomes,
- Men vaccinated during or before partners' pregnancies, and their pregnancy outcomes,
- Vaccinated women or men, and their potential experiences with infertility.

Consultants: Dr Roberta Ness and Dr Greg Poland